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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/205,658	12/03/1998	GARY RUVKUN	00786/351004	7404

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	18

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/205,658	RUVKUN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-17 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10-17 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response and Dr. Ruvkun's declaration filed on 11/25/02 has been acknowledged.

Claims 1 and 2 are amended.

Claims 1-5, 8, 10-17, 23 and 25-28 were pending and were examined in this office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 1-5, 12-15 and 23 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession of the claimed invention** for the same reasons of record as set forth in the office action mailed on 06/20/02.

The scope of invention as claimed encompasses any and all daf-18 nematode homologs and any and all mammalian PTEN genes. At best the specification as filed only discloses C.elegans daf-18 and human PTEN gene (spec. page 108, line 19). The instant specification fails to disclose any daf-18- homolog isolated from any and all nematodes. Similarly, instant specification fails to disclose PTEN-homolog isolated from any and all mammals. There is no description of mutational sites that exist in nature, and there is no description how the structure of nematode-daf-18 or human-PTEN relates to the structure of any other nematode or mammalian homologs respectively. The art at the time of filing teaches that daf-18 encodes a homolog of the human tumor suppressor PTEN (MMAC1/TEP1), which has 3-phosphatase

activity toward phosphatidylinositol 3,4,5-trisphosphate (Ogg et al, Mol. Cell 2:887-893, 1998, see abstract). In addition, the mammalian PTEN-like polypeptides include members that would expect to have widely divergent functional properties. The specification only disclosed nucleic and amino acid sequences encoding C.elegans daf-18 and human PTEN polypeptide. The specification fails to disclose nucleic and amino acid sequences encoding daf-18-like and/or PTEN-like protein obtained from any other animal. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In addition possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention Pfaff v. Wells Electronics, Inc 48 USPQ2d 1641, 1646 (1998). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Response to Arguments

The applicant argues that the specification discloses the nucleic acid and amino acid sequences of C. elegans daf-18 and human PTEN, which is sufficient to show that applicants were in possession of claimed genus (response, page 14). The applicant further argues that the specification teaches mutational sites and identifying characteristics of C. elegans daf-18 and human PTEN (response, page 15). Considering the sequence similarly (43%) the applicant argues that C. elegans daf-18 and human PTEN proteins are highly related and further presumes that other related nematode or mammalian daf-18/PTEN proteins would also substitute for C. elegans daf-18 (response page 15-16). The applicant argues that the conserved phosphatase

domain is a hallmark that is conserved among all daf-18/PTEN proteins, since human PTEN and C.elagans daf-18 are clearly representative of the genus as claimed (response page 19).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record see In re Scarbrough 182 USPQ, (CCPA) 1979. The scope of invention as claimed encompasses any and all daf-18 nematode homologs and any and all mammalian PTEN homologs. At best the specification as filed only disclose C.elegans daf-18 and human PTEN gene (spec. page 108, line 19). Besides C. elagans daf-18 the specification as filed fails to disclose singe daf-18-homolog isolated from other nematodes. Similarly besides human PTEN the specification as filed fails to disclose single PTEN homolog isolated from any other mammal. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USP2d 1481 at 1483. In Fiddes, claims directed to a mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Accordingly the instant specification as filed only disclosed C. elegans daf-18 and human PTEN sequences, which clearly lacks of written description for that broad class as claimed.

Even though the applicant argues that C. elegans daf-18 share sequence similarities with rat, mouse and human, the declaration fails to disclose a single daf-18 homolog obtained from all known nematodes (other that C.elegans). Furthermore based upon low sequence similarly one skill in the art would not expect that all mammalian PTEN homologs would have PIP3 specific phosphatase activity. The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian

insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).* In the instant case the nematode daf-18 and mammalian PTEN has been defined only by a statement of function of PIP3 specific phosphatase activity, which conveyed no distinguishing information about the identity of the claimed DNA/amino acid sequences, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

2. Claims 1-5, 8 and 10-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that modulates C.elegans DAF-18 or human PTEN expression or activity in C. elegans or isolated mammalian cells, does not reasonably provide enablement for a method for identifying a compound that modulates DAF-18 or PTEN expression or activity, wherein the DAF-18 and PTEN are obtained from any and all nematodes or mammals respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims for the same reasons of record as set forth in the office action mailed on 06/20/02.

Nature Of Invention: The invention is drawn to methods for identifying candidate compounds that modulate nematode Daf-18 and mammalian PTEN expression or activity in a nematode, isolated nematode cell or isolated mammalian cell, wherein the compound is a candidate compound for ameliorating or delaying impaired glucose tolerance condition or obesity or increase longevity of a cell or an organism.

Breadth Of Claims And Guidance Provided By The Inventor: The instant claims are drawn to a method for identifying compound that modulates nematode Daf-18 expression or activity in a nematode, isolated nematode cell or isolated mammalian cell. The claims are drawn to a method a method for identifying compound that modulates mammalian PTEN expression or activity in a nematode, isolated nematode cell or isolated mammalian cell. The specification as filed only discloses C.elegans daf-18 and human PTEN genes. The instant specification fails to disclose any daf-18- homolog isolated from any and all nematodes (spec. page 108, line 19). Similarly, instant specification fails to disclose PTEN-homolog isolated from any and all mammals, other than human PTEN (spec. page 108, line 19). The specification fails to disclose how the structure of C.elegans-daf-18 or human-PTEN relates to the structure of any other neamtode or mammalian homologs.

State Of Art And Predictability: The art at the time of filing teaches that daf-18 encodes a homolog of the human tumor suppressor PTEN (MMAC1/TEP1), which has 3-phosphatase activity toward phosphatidylinositol 3,4,5-trisphosphate (Ogg et al, Mol. Cell 2:887-893, 1998, see abstract). Furthermore, the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans (Larsan et al, Genetics 139:1567-83, 1995; ref of record). Furthermore, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Considering the fact that C.elagans daf-18 is only 43% identical to human PTEN protein (see Dr. Ruvkun's declaration) the instant specification fails to provide a single working example that that demonstrated that human PTEN would substitute the function of C. elagans daf-18 in C.elegans cellular micro-environment. Therefore it is even highly unpredictable that any mammalian PTEN would substitute the function of daf-18 in any and all nematodes (other than C.elegans). Similarly, in view of applicant's disclosure it is highly unpredictable that human PTEN would substitute the function of PTEN isolated from any and all mammals (other than humans).

Therefore, it is concluded that applicant has not presented enablement commensurate in scope with the claims.

Response to Arguments

The applicant fails to address this rejection in the response filed 11/125/02. However considering the applicants response regarding written description rejection above the instant claims stand rejected for the reasons of record as set forth in the office action mailed on 06/20/02 and as set forth above in the written description rejection. In instant case screening candidate compounds that modulates nematode daf-18 or mammalian PTEN in any and all specie of nematodes is not considered routine in the art and without sufficient guidance to a specific daf-18/PTEN-host interaction the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the unpredictability in the art and the limited guidance provided in the specification as filed one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making and testing nematodes and recombinant mammalian cells expressing daf-18 or PTEN nucleotide sequences isolated form any and all species of nematodes or mammals respectively.

3. Claims 23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic C. elegans whose cells contain a transgene encoding human PTEN polypeptide, does not reasonably provide enablement for any and all nematodes whose cells contain a transgene encoding any and all mammalian PTEN polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the office action mailed on 06/20/02.

Nature Of Invention: The invention as claimed is drawn to a transgenic nematode encoding mammalian PTEN polypeptide.

Breadth Of Claims And Guidance Provided By The Inventor: The scope of invention as claimed encompasses any and all transgenic nematodes encoding any and all mammalian PTEN polypeptides. The specification as filed fails to disclose a single transgenic nematode whose cells contain a transgene encoding mammalian PTEN. *At best Dr. Ruvkun's declaration filed on Paper No. 14 (07/14/00) only disclosed a transgenic C.elegans whose cells contain a transgene encoding human PTEN polypeptide* (declaration, page 2, para.6).

State Of Art And Predictability: The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). In instant case, the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans (Larsan et al, Genetics 139:1567-83, 1995; ref of record). The specification fails to provide any guidance that the structure of C.elegans-daf-18 or human-PTEN relates to the structure of any other neamtode or mammalian homologs. The lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall RJ Theriogenology 45:57-68, 1996, page 61-62, ref of record). Cis acting elements of one species may interact with different transactivating factors in other species. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic

animal are greatly dependent upon the specific expression vector used. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, 548). Therefore considering the state of transgenic art and limited disclosure the applicant has only enabled for a transgenic C.elegans whose cells contain a transgene encoding human PTEN polypeptide. Making any and all transgenic nematodes (other than C.elegans) is considered highly unpredictable, since the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans.

Response to Arguments

The applicant argues that the references cited in the support of lack of enablement are not relevant since invention is drawn to transgenic nematodes and not to transgenic mice (response, pages 20-23). The applicant argues that making transgenic nematodes is a routine matter, since transgenic C.elegans can be made by microinjecting plasmid or linear DNA. (response page 24 para.1). Even though the applicant argues that the making transgenic nematodes is different from making transgenic mice, the references cited in the office action clearly emphasize that the phenotype of an animal is determined by a complex interaction of genetics and environment, wherein the collection of all genes present in an organism influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Therefore making any and species of nematode (other than C.elegans) is considered highly unpredictable, since the genetic interaction among various DAF genes and/or gene products is complex and is only well studied in C.elegans. The specification fails to disclose any other nematode wherein the daf-18 related biochemical pathway has been well studied. Furthermore, nematodes are one of the most widespread and abundant groups of animal encompassing approximately 12,000 species. Making any and all transgenic nematodes selected from such a collection is not considered routine in the art and without sufficient guidance to a specific daf-18/PTEN-host interactions, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the unpredictability in the art and the limited guidance provided in the specification

as filed one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making of any and all transgenic nematodes encoding any and all mammalian PTEN genes.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER